AN EVALUATION IN THE SCREENING AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS AMONG LOW AND HIGH RISK OBSTETRICS POPULATION

BY : DR ASMAH YUN BTE MAT SIDEK

Dissertation Submitted In Partial Fulfillment Of The Requirement For The Degree Of Master Of Medicine (Obstetrics & Gynaecology)

UNIVERSITI SAINS MALAYSIA
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Final thanks must go to all patients to whom this book is dedicated to.

Nov 2001 Dr Asmah Yun Bte Mat Sidek

INTRODUCTION TO THE HOSPITAL KUALA TRENGGANU

The state of Terengganu is located in the East Coast of Peninsular Malaysia, facing the South China Sea covering 1,295,517.1 kilometers square. With stretches of white sandy beaches along the coast, make Terengganu one of the most popular tourist destinations. The main economical activities are fisheries and petroleum industry.

Kuala Terengganu Hospital, which is the only referral hospital for the state, also serves 7 districts. It is located about 2 kilometers away from the town of Kuala Terengganu and has a total of 786 beds. The hospital is made up of 2 main areas, i.e. the new 8-storey hospital complex and the old hospital block where both are facing the beautiful South China Sea.

The Obstetric and Gynaecology Department is functioning with 2 consultants, 2 clinical specialists, 3 medical officers, 7 posts graduate master candidates of University Sains Malaysia and University Kebangsaan Malaysia and 12 house officers. There are also one matron, 4 sisters, 78 nurses and 64 support staff.

MATERNITY COMPLEX (OBSTETRIC SECTION)

Obstetric section is situated mainly at level 1 and partly at the ground flour and level 2 of the main building. It includes the clinics, Day care center, Admission center, Antenatal ward, Postnatal ward, Labour suites and maternity Operation Theatre.

There are 4 wards to accommodate the obstetric patients, 1 antenatal ward (36 bedded), 2 postnatal wards (36 bedded-high risk ward and 24 bedded – low risk ward) and 1 first class ward (10 bedded mixed Obstetric ward). Admission centre served to ensure appropriate admission and also minimize delay in clerking. In 1999 the centre received 13 094 patients. The Bed Occupancy Rate for the antenatal ward is almost always above 100%.

The Labour Suite has 12 delivery beds where 3 beds are reserved for patients requiring close monitoring during tocolytic therapy or bleeding placenta praevia in which expectant management is carried out. Besides that, there is a 2 bedded room for patients with severe Pre-eclampsia/ Eclampsia room(PE room).

This hospital also adopts the 'husband friendly hospital'. The response is good and an average of 150 husbands will be with their wives during labour every month.
Adjoining to the labour suite is the maternity theatre where elective and emergency Caesarean section are carried out from 8.00 am to 3.00 pm. The services is run by 5 dedicated maternity staff.

The Day care service has reduced the number of clinic attendance and unnecessary admission. In 1999 there were 1466 attendance to the day care centre . There are 3 antenatal clinic sessions per week i.e. antenatal booking, combined clinic and antenatal follow up clinic. There is also 1 postnatal clinic session weekly. The total attendance annually is about 10,000.

GYNAECOLOGY SECTION

Gynaecology also contributes to the workload in the Department. Besides having the gynaecology clinic, the specialised clinic, Infertility and Intrauterine insemination method, oncology, molar and colposcopy are also available. The total attendance for the gynae clinic is more than 5000 patients per year.

ABSTRAK

Objectif *: Kajian di jalankan untuk menentukan prevalen kes-kes kencing manis semasa hamil di kalangan populasi obstetrik Hospital Kuala Trengganu mneggunakan kaedah MOGTT membezakan kriteria WHO 1985 dan 1998. Perbandingan komplikasi kepada ibu dan bayi juga di ambil kira. Tujuan kedua adalah untuk mengira nilai-nilai ramalan keatas cara-cara pengesanan kes kencing manis ketika hamil yang di namakan sebagai Glucose Challenge Test (GCT), ciri-ciri potensi untuk mengidap kencing manis ketika hamil dan Fasting Plasma Glucose (FPG). Akhir sekali, kajian ini bertujuan menentukan prevalen kes kencing manis yang berpanjangan selepas 6 minggu kelahiran.*

Metodologi *: Kajian kohort prospective dan observasi di lalukan antara bulan Julai ke November 1999 di Unit Obstetrik, Hospital Kuala Terengganu. Pesakit antenatal di bahagi kepada dua kumpulan mengikut kehadiran ciri-ciri potensi menghidap kencing manis semasa hamil (iaitu kumpulan berisiko rendah dan tinggi). Ujian GCT di jalankan kepada kumpulan berisiko rendah di ikuti dengan ujian MOGTT selepas satu atau dua minggu berikutnya. Semua pesakit di dalam kumpulan berisiko tinggi di beri tarikh untuk ujian MOGTT. Paras gula >7.2mmol/l di kira sebagai positive untuk ujian GCT. Keputusan ujian MOGTT di analisa menggunakan kriteria WHO 1985 dan 1998. Pesakit yang menghidap kencing manis semasa hamil di rawat mengikut protokol yang di sediakan oleh hospital. Mereka di awasi sehingga bersalin atau akan di masukkan ke wad pada 38 minggu kehamilan untuk di paksa bersalin. Rekod bayi di ambil. Akhirnya mereka di beri tarikh untuk mengulangi ujian MOGTT selepas 6*

minggu kelahiran. Data di ananlisa menggunakan SPSS versi ke-9. Ujian Chi-square dan Student t di gunakan untuk mengetahui signifikasi kajian. Keputusan paras p < 0.05 di kira sebagai signifikan.

***Keputusan**: Dari 757 wanita, hanya 671 dari mereka dapat melengkapkan kajian. Prevalen kes kencing manis semasa hamil ialah 9.5%(64 dari 671) menggunakan kriteria WHO-1985 dan 10.3%(69 dari 671) menggunakan kriteria WHO-1998. Seramai 22 orang dari 199 pesakit berisiko rendah mempunyai keputusan GCT yang positive dan sepuluh (6.0%) mengalami kencing manis semasa hamil. Dari 472 pesakit di dalam kumpulam berisiko tinggi, 54(11.4%) dari mereka di kesan mengidap kencing manis semasa hamil mengikut kriteria WHO-1985 dan 59 (12.5%) mengikut kriteria WHO-1998. Tiada perbezaan di dalam data demografic dan komplikasi ke atas ibu dan bayi di antara dua kriteria. Pesakit kencing manis semasa hamil di dapati berisiko untuk mengalami penyakit tekanan darah tinggi semasa hamil, insiden kelahiran paksa dan kaedah kelahiran secara caesarean. Bayi di kalangan mereka di dapati lebih berat dan insiden berat bayi melebihi 4 kg adalah signifikan. Tetapi tiada perbezaan di dalam kelahiran kurang matang, kecacatan semulajadi, kelahiran mati dan kelahiran sangkut bahu. Prevalen kes kencing manis yang berpanjangan selepas 6 minggu kelahiran adalah 26.9% dari kalangan pengidap kemcing manis semasa hamil. Nilai sensitiviti bagi kaedah GCT, satu ciri potensi , lebih dari satu ciri potensi untuk kencing manis semasa hamil dan FPG adalah 90.0%, 68.8%, 76.2% dan 14.5%. Nilai spefisiti bagi ujian yang sama adalah 93.6%, 35.6%, 75.9% dan 100%. Nilai ramalan positif adalah 42.8%, 6.0%, 29.6% dan 95%. Nilai ramalan negatif adalah 99.4%, 100%, 100% dan 91.9%.*

***Kesimpulan**: Prevalen kes kencing manis semasa hamil di dalam populasi ini dalah setara jika di bandingkan dengan ujina–ujian setempat terdahulu. Prevalen menggunakan kriteria WHO-1998 di dapati tinggi sedikit berbanding kriteria WHO-1985. Tetapi tiada perbezaan data demografik, komplikasi ke atas ibu dan bayi di antara kedua kriteria melainkan jika di bandingkan dengan ibu-ibu yang tidak mangidap kencing manis semasa hamil. Perbezaan yang ketara di lihat untuk cara pengesanan kencong manis semasa hamil dan di dapati cara GCT mempunyai nilai-nilai ramalan yang terbaik secara keseluruhan. Prevalen penyakit kencing manis yang berpanjangan 6 minggu selepas kelahiran di dapati rendah sedikit jika di bandingkan dengan kajian terdahulu mungkin di sebabkan kehadiran yang sangat kurang untuk mengulangi ujian MOGTT.*

ABSTRACT

***Objective**: The study is aimed to determine the prevalence, maternal and fetal outcome of gestational diabetes mellitus among low and high risk hospital base obstetric population using MOGTT WHO-1985 and 1998 criteria. Secondly we aimed to determine the predictive value of three different methods of GDM screening (namely the GCT, potential diabetic picture and fasting plasma glucose). Lastly, we planned to determine the prevalence of persistent diabetes at 6 weeks post-partum among studied GDM patients.*

***Methodology**: A prospective cohort and observational study was conducted from July till November 1999 in an Obstetric Unit Hospital Kuala Terengganu. An antenatal patient between 22 to 36 weeks gestations were divided into two groups depending on presence of clinical risk factors for developing GDM (i.e. low and high risk). GCT was performed upon low risk patients followed by MOGTT one to two weeks later. All patients in high-risk group were given appointment for MOGTT. GCT of 7.2 mmol/l or more were considered positive. MOGTT results were analysed by using WHO-1985 and 1998 criteria. Those patients with GDM were managed according to hospital protocol. They were followed-up till delivery or admitted at 38 weeks for induction of labour. Babies notes were recorded and lastly, those patients with GDM were given appointment to repeat MOGTT at 6 weeks post-partum. Data were analysed by SPSS version 9. Chi-square and Student t test used to assess the significance. P value of < 0.05 considered significant.*

***Results**: Out of 757 women, only 671 completed the study. The prevalence of gestational diabetes mellitus in this studied population is 9.5%(64 out of 671) by WHO*

1985 and 10.3% (69 out of 671) by WHO-1998 (P value <0.05). There were 199 low risk patients in which 22 were positive for GCT and 10 of them (6.0%) were GDM. Fifty-four (11.4%) out of 472 high-risk patients were GDM using WHO-1985 and 59(12.5%) by using WHO-1998. Their characteristics are not significantly different. GDM patients were significantly associated with PIH, induced labour and increased risk of caesarean section. Offspring of GDM tend to be heavier and increased incidence to developed macrosomia. No difference in the incidence of premature delivery, stillbirth rates congenital abnormality, shoulder dystocia or prenatal mortality. The incidence of persistent diabetes 6 weeks post-partum is 26.9% in the diabetic picture GDM paitents. The sensitivity for the GCT (Blood sugar > 7.2 mmol/l), single risk factor, multiple risk factors and the FPG are 90.0%, 68.8%, 76.2%, 14.5% respectively. The specificity for them is 93.6%, 35.6%, 75.9% and 100% respectively. The positive predictive values are 42.8%, 6.0%, 26.9% and 95.0% respectively. The negative predictive values are 99.4%, 100%, 100% and 91.9% respectively.

Conclusion: *The prevalence of gestational diabetes mellitus in this studied population is comparable to other local studies. It shows slightly higher when using MOGTT WHO-1998 compared to WHO-1985 criteria. However there is no difference in all characteristics and outcome measures unless when compared to non-GDM patients. The predictive values of three methods of GDM screening varied greatly, with the GCT being the best overall. Persistent diabetes 6 weeks post-partum were slightly lower to comparable study probably because poor turn-up for repeat MOGTT among previously diagnosed as GDM.*

ABBREVIATIONS

ADA	=	American Diabetic Association
AGA	=	Appropriate Gestational Age
APH	=	Antepartum Haemorrhage
BMI	=	Body Mass Index
BW	=	Birth Weight
BOH	=	Bad Obstetric History
DM	=	Established Diabetes Mellitus
FSB	=	Fresh Still Birth
FPG	=	Fasting Plasma Glucose
GDM	=	Gestational Diabetes Mellitus
GCT	=	Glucose Challenge Test
Hb AIC	=	Glycosylated Haemoglobin
IDDM	=	Insulin Dependent Diabetes Mellitus
IFG	=	Impaired Fasting Glucose
IUD	=	Intrauterine death
Kg/m2	=	Kilogram per meter square
Kg	=	Kilogram
LGA	=	Large for Gestational Age
LSCS	=	Lower Segment Caesarean Section
MOGTT	=	Modified Oral Glucose Tolerance Test

MMR	=	Maternal Mortality Rate
Mmol/l	=	milimol per litre
MSB	=	Macerated Still Birth
NIDDM	=	Non Insulin Diabetes Mellitus
NDG	=	National Diabetic Group
NS	=	Non Significant
NPV	=	Negative predictive value
POA	=	Period Of Amenorrhoea
POG	=	Period Of Gestation
PMR	=	Perinatal Mortality Rate
PE	=	Pre-Eclampsia
PPV	=	Positive pedictive value
SGA	=	Small Gestational Age
Wk	=	week

1. INTRODUCTION TO GESTATIONAL DIABETES MELLITUS.

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Coustan DR et al, 1998). The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognised glucose intolerance may have antedated or begun concomitantly with the pregnancy.

The diagnosis of GDM has implications affecting both the pregnancy and the future health of the mother and the fetus. Despite adverse clinical sequelae, there remains ambiguity and uncertainty amongst Obstetricians and Physicians on the importance of the screening and diagnosing of GDM. Controversy also exists in the management of the pregnancy complicates by diabetes.

Although the benefits of careful regulation of maternal glycaemia is well accepted, questions remain regarding those factors which contribute to intrauterine death and congenital malformations, as well as significant neonatal morbidity observed in the infant of the diabetic mother. There are also debates concerning the need and timing of obstetric interventions, including the assessment of foetal well being and maturity. If the preventative health measures are to be effective in reducing the long-term morbidity of GDM, the problems surrounding its diagnosis and screening need to be addressed.

1.1 PREVALENCE OF GESTATIONAL DIABETES MELLITUS

Approximately 4% of all pregnancies are complicated by GDM, resulting in 135,000 cases annually in United States (Franz MJ, 1994). The prevalence may range from 1 to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed. Compared to white/European women, the prevalence rate for GDM is increased approximately eleven folds in women from the Indian subcontinent, eight folds in South East Asian women and six and three folds in Arab/Mediterranean and black/Afro-Caribbean women, respectively (Dornhorst A et al, 1992). Study done by T.T. Lao et al in 1998, the prevalence among Chinese and Asian populations using WHO-1985 criteria was 11%, but 95% of their cases fell into the category of Impaired Glucose Tolerance (IGT) in pregnancy. The prevalence of gestational diabetes highly dependent on ethnicity. Increasing maternal obesity, age and family history of diabetes are additional important independent risks for GDM (Shelley-Jones 1993).

In the study done in Kuala Lumpur Hospital by Kamal Bahrin AR et.al (1990), among the obstetric population, 500 patients out of 3885 study sample had risk factors for GDM and 107 (21.4%) had abnormal Glucose Tolerance Test, using WHO-1985 criteria. Seventy nine (15.8%) were IGGT and 28(5.6%) had diabetic picture out side pregnancy. Premitha et al, 1993 noted 343 (12.7%) out of 2690 studied population in University Hospital having GDM and 54 (15.5%) of these women did not have any known risk factors.

1.2 AETIOLOGY OF GESTATIONAL DIABETES MELLITUS

From an aetiology perspective, there are three subgroups of gestational diabetes: previously undiagnosed abnormal glucose tolerance; pregnancy induced glucose intolerance and rarely the early autoimmune beta-cell-destruction phase of insulin-dependent diabetes mellitus (IDDM).

After delivery, women in the first group will have impaired glucose tolerance or non-insulin-dependent diabetes mellitus (NIDDM), those in second group will have normal glucose tolerance but has higher risk of NIDDM in the future. Those in the third group will have IDDM, most within two years.

This clinical spectrum of gestational diabetes is highly dependent on the local prevalence of impaired glucose tolerance and NIDDM, and on the other variables such as ethnic background, age and basal metabolic (Nelson-Piercy C et al, 1993).

1.3 PATHOPHYSIOLOGY OF GESTATIONAL DIABETES MELLITUS AND ITS COMPLICATIONS.

During normal pregnancy, maternal metabolism adjusts to provide adequate nutrition to both the mother and growing fetoplacental unit. Early in pregnancy, glucose homeostasis is affected by increases in oestrogen and progesterone, which lead to B cell hyperplasia, and increase in insulin secretion. Increase in peripheral utilisation of glucose result in lower maternal fasting glucose levels. Glycogen deposition increase in peripheral tissues, accompanied by decrease in hepatic glucose production. Insulin-dependent diabetics therefore commonly experience periods of hypoglycaemia in the first trimester. Additionally, maternal circulating levels of fatty acids, triglycerides, and ketones are increased. Maternal mechanisms to offset this state "accelerated starvation" include increased in protein catabolism and accelerated renal gluconeogenesis.

Lipids become an important maternal fuel as pregnancy advances. In early pregnancy, fat storage increases. With the rise of human placental lactogen (hPL), a polypeptide hormone produced by syncytiotrophoblast, lypolysis is stimulated in adipose tissue. The release of glycerol and fatty acids reduces both maternal glucose and amino acid utilization, and in doing so, spares this fuel for the foetus. The action of hPL is responsible, in part, for the 'diabetogenic state' of pregnancy. In the normal pregnant women, glucose homeostasis is maintained by an exaggerated rate and the amount of insulin release reaching almost twice the non-pregnant level., which later accompanies with decreased sensitivity to insulin and

blood glucose are kept within a very narrow range of between 4 and 6 mmol/l during much of every 24 hours (Kuhl 1984). Other hormones, which appear to modify this response, include elevated levels of free cortisol, oestrogen and progesterone (Marest M et al 1995).

With placental growth, larger amounts of anti-insulin factors are synthesized. A women with overt diabetes cannot respond to this stress and requires additional insulin requirement, approximately 30% to the pre-pregnancy dose, is roughly equivalent to the endogenous increase seen in normal gestation (Gillmer M.D.G et al, 1999).

From 10 to 16 weeks, the fasting level of glucose is significantly lower than the non-pregnant level and there is a slow but significant rise up to 33 weeks. Thereafter the fasting level falls again slowly so that at term it is not significantly different from the non-pregnant level (Baird 1986). The peak levels of glucose after a carbohydrate load are higher than non-pregnant especially after the 20^{th} weeks.

The vast majority of pregnant women manage to maintain their blood glucose within normal limit but around 2% cannot do so, and become hyperglycaemic, similarly a further 2% hypoglycaemic. The consequences of this increasing resistance to insulin activity is that eventually, usually late in the second trimester of pregnancy, the capacity for insulin secretion is exceeded resulting in impairment of glucose tolerance and gestational diabetic in the women so destined.

Maternal hyperglycaemia is an important contributor to accelerated foetal growth and the development of the large for gestational age infant. The foetal B-cells respond as early as 11 weeks gestation to maternal hyperglycaemia. Foetal insulin is an anabolic hormone and causes visceral enlargement and excess fat deposition in human and experimental animals. There is ample evidence that maternal hyperglycaemia and the resulting foetal hyperinsulinaemia have a permissive effect on the foetal growth patterns, with the greatest influence being seen between 28 and 32 weeks. This anabolic effect also influenced by the genetic factor, with certain ethnic groups being more susceptible to the growth promoting effects of hyperglycaemia. More importantly, maternal factors including age, body weight and parity independently contribute to increasing birth weight (Dornhorst A et al, 1998).

Studies of chronic hyperglycaemia in pregnant sheep have shown increased aerobic and anaerobic glucose metabolism causing increased oxygen consumption, lactate production and fall in pH and oxygen tension. Three changes are thought to be the most likely the causes of the sudden foetal death that may occur late in diabetic pregnancy. Analyses of human umbilical cord blood have confirmed significant associations between maternal blood glucose and foetal insulin concentrations and the degree of foetal acidemia. In addition, the combination of foetal hyperinsulinaemia and foetal hypoxia appears to stimulate both foetal medullar and extramedullary erythropoiesis causing polycythaemia possibly as a result of increased foetal erythropoeitin levels.

Foetal hyperinsulinaemia also predisposes to a variety of effects observed in the neonate hypoglycaemia, respiratory distress syndrome and jaundice. These latter two complications appear to be due to inhibition of the effect of cortisol on the enzyme systems concerned with the surfactant production by the foetal lungs and the development of microsomal enzyme systems within the foetal liver.

Several obstetric problems occur more commonly in diabetic pregnancy, their frequency being directly related to the quality of the diabetic control achieved. The most common feature of poorly controlled diabetes is polyhydramnios, which can occur due to a foetal osmotic diuresis induced by maternofetal hyperglycaemia. Besides that they are also prone to get infections especially urinary and genital tract infection particularly candidiasis. Premature contraction occurs in up to 20% of diabetic pregnancies and may occasionally be associated with polyhydramnios and infections. Pre-eclampsia occurs approximately twice as frequently in diabetic as non-diabetic pregnancies. Serial serum creatinine and urate concentrations and 24 hour urine protein measurements provide early biochemical evidence of proteinuric pre-eclampsia and also help to differentiate between pregnancy induced hypertension and pre-existing hypertension masked by pregnancy.

1.4 SCREEENING OF GDM, DOES IT IMPROVE MATERNAL AND PERINATAL OUTCOME?

Screening for gestational diabetes remains extremely controversial. There is much debate worldwide as to whether women should be screened for GDM at all, only high-risk women should be screened, or universal screening for all pregnant women should be the standard for care.

The short term benefits of screening and treating gestational diabetes have focused on pregnancy outcome. In high-risk populations, with a high background prevalence of diabetes combined with limited access to medical and perinatal care, perinatal mortality can be seen to improve after screening for and treatment of gestational diabetes. Retrospective studies suggest a benefit on stillbirth rates after the introduction of screening and treating gestational diabetes in low risk populations, but demonstrating a benefit on perinatal mortality in prospective trials has proved to be more difficult. In Western populations, with a low prevalence of diabetes, good access to medical care, and low perinatal mortality and morbidity rates, there are ethical constraints in mounting randomised trials with sufficient power to test whether treating gestational diabetes reduces perinatal morbidity. Prospective studies in these populations have therefore assessed pregnancy outcome using surrogate markers of diabetic control. These include macrosomia, need for caesarean section and fetal hypoglycaemia. None of these end points are specific for diabetes and many are influenced by the practice of individual obstetricians, maternal obesity, age, and parity.

Much confusion in terms of who should be screened, how to screen, and the management of those with positive results. Confusion arises from lack of or poor quality evidence, compounded in this instance by a concept that gestational diabetes mellitus found on risk of subsequent non-insulin dependent diabetes mellitus rather than outcome of the index pregnancy. In addition, the criteria for gestational diabetes prescribe a minimum, but not a maximum, level of glucose intolerance, so that any group of women labelled as having gestational diabetes might contain some with glycaemia in the range that qualifies for a diagnosis of non-insulin dependent diabetes, rendering comparisons of different series impossible. R J Jarrett et al (1997) suggested four questions, which required answers to achieve resolution: How severe must maternal hyperglycaemia be to measurably worsen pregnancy outcome? Can we intervene to prevent adverse outcomes? Is such intervention cost effective? If so, what is the most appropriate way of screening and detecting the problem? (R J Jarrett et al, 1997).

Opponents of screening argue that it incurs significant financial costs and stressful burden on healthcare institutions, society and women, without usefully altering the prenatal outcome. The diagnostic label of GDM sensitises obstetricians, thereby increasing the number of interventions and caesarean delivery even though the weight of the baby is appropriate-for gestational-age infants.

Proponents of screening argue that the primary benefit lies in the early identification of women at risk for developing type 2 diabetes mellitus. Early identification may help modify the natural history of type 2 diabetes mellitus and thus prevent diabetic

complications. The focus has now shifted to the perinatal risks associated with GDM rather than the long-term effects. Many retrospective and prospective studies have suggested convincingly that there is an association between carbohydrate intolerance and perinatal complications, in particular foetal macrosomia and resultant shoulder dystocia and caesarean delivery.

Those who do not favour screening for gestational diabetes claim, among other things, that the current screening and diagnostic strategies are cumbersome. In this issue Perucchini et al (1999), propose a protocol, which could counter this argument: they suggest using a fasting glucose value as a screen for gestational diabetes. This protocol differs from the two currently recommended procedures.

Attempts to detect unrecognised diabetes in pregnancy are a part of established practice in every antenatal clinic in this country. The justification for this is the possible increased in risk of perinatal death amongst women who have an abnormal GTT in pregnancy. The success of these efforts varied widely because of the generalised lack of any consistent and systemic approach to the problem. If screening is to be effective it must be comprehensive, needs to reflect the ethnicity of the population, the availability of health care, and the economic and medicolegal expectations of the country. Once the decision has been made to screen, a reproducible screening test needs to be chosen that is sensitive, specific and easily applied. Many screening systems have been advocated but a few are worthy of consideration for the reasons given above.

1.4.1 ORAL GLUCOSE CHALLENGE TEST

The most universally researched screening test is the O'Sullivan test, which involves One-hour time blood glucose sample after a 50 g Oral glucose load. Soarse et al in 1997, stated the overall sensitivity was 95% and specificity 85% for detecting pregnancy induced glucose intolerance that occurred at 20-28 weeks gestation.

A first trimester test is advisable in high-risk patient, in which more women will have GDM before 20 weeks. A cut off value of 7.8 mmol/l is most commonly used. If this level is used, approximately 14% of the population will require an OGTT and the diagnosis of GDM will be missed in approximately 10% of the affected population (Coustan et al, 1989). If a cut off value of 7.2 mmol/l were used, virtually all cases all GDM would be identified, but 23% of the pregnant population will require an OGTT (Coustan et al, 1990).

A cut off value of 7.8 mmol/l yielded a sensitivity of 59% and a specificity of 91% (Table 1.4.1). A cut off value of 7.5 mmol/l, as used by several investigators, yielded a sensitivity of 61% and specificity of 88%. The best cut off value for the 50 g screening test in Soarse et all, 1997, was 7.2 mmol/l (sensitivity 68%, specificity 82%). Thirty eight per cent of the women reported food intake up to 1 hour before the challenge test, 32% (167) between 1 and 2 hours before, and 27% (141) >2 hours before; 13 women did not report the time of last food intake. Analysis of the data for the women with food intake > 2 hours before the challenge test suggested that the sensitivity of the

1.4.2 FASTING PLASMA GLUCOSE

It has been recently compared with other measures of hyperglycaemia, and was found to be the best single test for diagnosing diabetes because its simplicity, low cost, reproducibility, and world wide availability. Its has been recently recommended as the most important diagnostic tool for the diabetes in non pregnant adult (ADA, 1997; WHO, 1998).

In this recommendation, the cut off point for the diagnosis of diabetes with fasting plasma glucose has been lowered to 7.0 mmol/l. If this cut point were to be applied to pregnancy, fasting glucose could serve as screening and a diagnostic tool, a strategy that could potentially improve early diagnosis at a lower cost.

Combining fasting blood glucose with potential diabetic picture has been found to have sensitivity of 90 % but the specificity of about 50%. However, that the diagnosis of gestational diabetes with fasting plasma glucose still awaits validation against obstetric outcome.

Other screening test, include random glucose values, glucosuria, fructosamine, diurnal glucose profiles, and glucose responses to mixed meals have been less extensively evaluated in pregnancy than the O'Sullivan test, which remains the gold standard. The sensitivity of purely clinical risk factors is poor, <70%, especially in multiethnic populations, since they do not include ethnicity.

1.4.3. POTENTIAL DIABETIC FEATURES

The commonest approach to screening for gestational diabetes has been to perform glucose tolerance test on women with defined potential diabetic features (i.e. clinical history aand current problems during pregnancy). On one hand this may result in 37% of the population requiring glucose tolerance test as approximately one in three antenatal patients has potential features of diabetes in her history, or the other chemical diabetes may arise in women without potential diabetic features (O'Sullivan et al 1973).

This method has a false-negative rate of about one-third (O'Sullivan et al. 1973, Gillmer et al. 1980). Furthermore, the potential diabetic features is equally distributed in the normal and abnormal glucose tolerance population. Reed (1984) estimated that 20% of the patients with gestational diabetes will be missed with this original method. Carpenter and Coustan (1982) modified the method by lowering the test threshold at the expense of test specificity.

1.5 STANDARD REFERENCE TESTS FOR GESTATIONAL DIABETES MELLITUS

Commonly accepted diagnostic criteria for diabetes mellitus were developed by the National Diabetes Data Group (NDDG) in 1979 (Diabetes 1979) and the World Health Organisation (WHO) in 1980 and updated in 1985 (WHO Tech Rep Ser 1980 & 1985) (Table 2). During it annual meeting in 1997, the American Diabetes Association (ADA) approved new diagnostic criteria for diabetes mellitus. On the basis of data from three different populations the intention was to identify the fasting blood glucose concentration that best predicted the risk developing microvascular complications. The revised criteria are symptoms of diabetes and a random plasma glucose concentration > 11.1mmol/l or a fasting plasma glucose > 7.0mmol/l or 2 hour plasma glucose > 11.1 mmol/l during a standard 75 g oral glucose tolerance test, as previously recommended by ADA and NDDG, approved by WHO (DECODE Study- Wareharm and O'Rahilly et al, 2000).

The main changes are the diagnostic fasting plasma (blood) glucose value has been lowered to > 7.0 mmol /l. A new category of Impaired Fasting Glycaemia (IFG) is proposed to encompass values which are above normal but below the diagnostic cut-off for diabetes (plasma > 6.1 to <7.0 mmol/l; for the whole blood > or =5.6 to <6.1 mmol/l (Peter G Colman et al, 1999).

Table 1.5 The Recommendations of diagnostic criteria for Diabetes Mellitus by WHO and ADA.

Diagnostic criteria (mmol/l)	WHO 1985 (Annex 2)	WHO 1998	NDDG-100 g Glucose load (Annex 3)	NDDG- 75 g Glucose load (Annex 4)
DM				
0 h	7.8	7.0	5.3	5.3
1 h	-	-	10.0	10.0
2 h	11.1	11.1	8.6	8.6
3 h	-	-	7.8	-
IGT				
0 h	< 7.8	< 7.0	-	-
2 h	7.8-11.0	7.8-11.0	-	-
IFG	-	6.1-6.9	-	-

This changes are based primarily on cross-sectional studies demonstrating the presence of microvascular (McCance DR et al, 1994) and macrovascular complications at these lower glucose concentrations (Charles MA et al,Lancet 1996). In addition, the 1985 WHO diagnostic criteria for diabetes based on fasting plasma level of > 7.8 mmol/l represents a greater degree of hyperglycaemia than the criteria based on plasma glucose level two hours after a 75 g glucose load of > 11.1 mmol/l (Finch CF et al, 1990). A fasting plasma glucose

level of >7 mmol/l accords more closely with this 2 hour post-glucose level. Epidemiological data from 20 European studies found that fasting plasma glucose of 7.0 mmol/l or more, predicted a diabetic 2 hour-plasma glucose with a sensitivity of 49.0% and specificity of 98.2% (DECODE Study, 1999).

Previously, the oral glucose test (OGTT) was recommended in people with a fasting plasma glucose level of 5.5-7.7 mmol/l or random plasma glucose level of 7.8-11.0 mmol/l. After a 75 g glucose load, those with a 2 hour plasma glucose level of < 7.8 mmol/l were classified as normoglycaemic, of 7.8-11.0 mmol/l as having impaired glucose tolerance and of > 11.1 mmol/l as having diabetes.

The new diagnostic criteria proposed by the ADA and WHO differ in their recommendation on use of the oral glucose tolerance test (OGTT). The ADA makes a strong recommendation that fasting plasma glucose level can be used on its own and that, in general, the OGTT need not be used (Diabetic Care, 1997). The WHO group argues strongly for the retention of the OGTT and suggests using fasting plasma glucose level alone only when circumstances prevent the performance of the OGTT. There are concerns that many people with fasting plasma glucose level< 7.0 mmol/l will have manifested abnormal result on the OGTT and are at risk of microvascular and macrovascular complications (Peter Gcolman et al, April 1999).

The conformational diagnostic test for gestational diabetes remains controversial. Glucose tolerance in pregnancy is a continuum; with no universally accepted criteria for defining the level at which glucose intolerance becomes abnormal and can be classified as GDM (Keen H, 1990). The lack of consensus for diagnosing GDM, has resulted in the WHO proposing the same diagnostic criteria be used for GDM as those for impaired glucose tolerance outside pregnancy, namely a 2 hours plasma glucose value greater than 7.8 mmol/l on the 75 g OGTT. Meaning that, pregnant women who meet WHO criteria for diabetes mellitus, or impaired glucose tolerance (IGT) are classified as having Gestational Diabetes Mellitus (GDM).

In the study by J.S.D. Nicholls et al, in 1995, showed that women who have GDM identified by WHO criteria have significant impairment of insulin release in respond to oral glucose tolerance test. He found that the WHO identifies women with a level of glucose intolerance, which is associated with a blunted and attenuated insulin response to oral glucose. Normal pregnancy requires that insulin release increase to counteract the physiological fall occurring in maternal insulin sensitivity. He suggest that it is the inability to adequately increase insulin secretion that is the cause of glucose intolerance of GDM, rather than a greater than expected fall in pregnancy related insulin sensitivity. The WHO criteria of GDM therefore identify women similar metabolic characteristics as described using the 100 g OGTT and the American National Diabetic Data Group (NDDG) criteria. In WHO new criteria (1998), defined GDM as the joint category of diabetes (fasting plasma glucose > 7.0 mmol/l or 2 hours glucose >11.0 mmol/l) and impaired glucose tolerance (IGT) (2 hours glucose > 7.8 mmol/l) first detected in pregnancy (Alberti

KGMM et al, 1998). Compared to previous recommendations, the fasting glucose cut-point has been lowered from 7.8 mmol/l to 7.0 mmol/l. However, its significance in pregnancy outcomes needs further evaluation. M.I. Schmidt et al (2000) described, of the 5004 pregnant women who completed an OGTT, 379 (7.6%) had GDM by 1998 criteria. Of these 379 cases, only 21 (5.5 %) had hyperglycaemia in the range considered diabetes mellitus outside pregnancy; the remaining 358 (94.5%) had IGT. Using the 1985 criteria, 378 cases of GDM were found, 15 in the diabetes range and 363 in the IGT. He concluded that the prevalence of GDM is minimally altered by the new WHO definition. Although GDM is a common condition, the vast majority of the cases have hyperglycaemia in the range considered impaired glucose tolerance outside pregnancy.

After the pregnancy ends, the women should be reclassified as having either diabetes mellitus, or IGT, or normal glucose tolerance based on the result of a 75 g OGTT six weeks or more after delivery. It should be emphasized that such women, regardless of the six-week post-pregnancy result, are at increased risk of subsequently developing diabetes. The significance of IFG by WHO new criteria in pregnancy remains to be established. Any women with IFG, however, should have a 75 g OGTT (K.G.M.M. Alberti et al, 1998).

1.6 CLINICAL PRACTICE RECOMMENDATIONS 2000 PRODUCED BY AMERICAN DIABETES ASSOCIATION: VOLUME 23 SUPPLEMENT 1

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM:

1.Marked obesity (BMI> 30kg/m2)

2.Personal history of GDM

3.Glycosuria,

4.Strong family history of diabetes

should undergo glucose testing as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation. Low-risk status requires no glucose testing, but this category is limited to those women meeting all of the following characteristics:

1. Age < 25 years
2. Weight normal before pregnancy
3. Member of an ethnic group with a low prevalence of GDM
4. Not known diabetes in first-degree relatives
5. No history of abnormal glucose tolerance
6. No history of poor obstetric outcome.

A fasting plasma glucose level >126 mg/dl (7.0 mmol/l) or a random plasma glucose >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge. In the absence of this degree of hyperglycaemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches:

1.6.1 One-step approach:

Perform a diagnostic oral glucose tolerance test (OGTT) without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or populations (e.g., some Native-American groups).

1.6.2 Two-step approach:

Perform an initial screening by measuring the plasma or serum glucose concentration 1 hour after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT.

When the two-step approach is employed, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cut-off of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the100-g OGTT are derived from the original work of O'Sullivan and Mahan, modified by Carpenter and Coustan (Annex 3), and are shown in Table 1.5. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 h, and 2 h; however, this test is not as well validated as the 100-g OGTT.

1.7 TREATMENT OF GESTATIOANL DIABETES MELLITUS

Women with gestational diabetes have two metabolic characteristic) impaired B-cell recognition of elevated glucose concentration, and ii) a delay in release of insulin. There are two treatment options: i) dietary treatment or ii) insulin treatment when dietary treatment alone is inadequate.

In normal weight GDM women, residual beta cell function is present and their problem is insufficient insulin reserve capacity to maintain normoglycaemia with meal stimulation. It is thereby physiological to give them a small dose of rapid-acting insulin before each meal.

In obese GDM women, the problem is different. In addition to the defects in beta cell function, they may have appreciable insulin resistance secondary to obesity that becomes more intense during pregnancy. They respond well to a reduction in caloric intake and preprandial doses of rapid-acting insulin.

Once the diagnosis of GDM is established, patients are begun on dietary program of 2000-2500 calories daily with the exclusion of simple carbohydrates (Hollingsworth 1992). Obese women with GDM may be managed on as little as 1200-1800 kcal/day with less weight gain and no apparent reduction in fetal size.

Tight maternal serum glucose control during 20^{th} to 30^{th} weeks of gestation can decrease the incidence of fetal macrosomia, however, good glycaemic control during the third trimester may not have similar effect (Langer 1989). Gestational diabetes may be safely followed until 40 weeks as long as the fasting and postprandial glucose values remain normal (Landon 1994).

1.7.1 ANTENATAL ASSESSMENT OF THE FETUS

Accurate information about the duration of pregnancy, fetal growth and fetal well being remains important. Ultrasound use in diabetic pregnancy is to measure the crown-rump length to confirm the duration of pregnancy. A biparietal diameter measurement should also be performed in the mid-trimester, ideally at 16 weeks gestation, to provide additional information about gestational age. Blood for serum alpha fetaprotein can also be taken at this gestation both to screen for neural tube defect and as part of "triple test" used to screen for Down syndrome.

A detail fetal examination to exclude congenital anomalies especially of neural, cardiac, renal system should be performed between 18 to 20 weeks, so that termination of the pregnancy can be considered, if appropriate. Serial growth based on measurements of the fetal head and abdominal circumference provide best means of identifying those fetus becoming macrosomic.

The non-stress test appears to be the preferred antepartum heart rate screening test in the management of patients with gestational diabetes (Landon 1990). In patients with poor control, in whom the incidence of abnormal test and intrauterine death is greater, testing is performed earlier in gestation and more frequent.

Biophysical profile did not appear to add more information about fetal condition if the non-stress test result was reactive, but a score of 8 based on ultrasound parameters was as reliable in predicting good fetal outcome as was a reactive non-stress test (Golde 1984).